

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Targretin 75 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg of bexarotene.

Excipient(s) with known effect: sorbitol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Off-white capsule, containing a liquid suspension and imprinted with “Targretin”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Targretin is indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients refractory to at least one systemic treatment.

4.2 Posology and method of administration

Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL.

Posology

The recommended initial dose is 300 mg/m²/day. Initial dose calculations according to body surface area are as follows:

Initial dose level (300 mg/m ² /day)		Number of 75 mg Targretin capsules
Body Surface Area (m ²)	Total daily dose (mg/day)	
0.88 – 1.12	300	4
1.13 - 1.37	375	5
1.38 - 1.62	450	6
1.63 - 1.87	525	7
1.88 - 2.12	600	8
2.13 - 2.37	675	9
2.38 - 2.62	750	10

Dose modification guidelines: the 300 mg/m²/day dose level may be adjusted to 200 mg/m²/day then to 100 mg/m²/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m²/day. Doses greater than 650 mg/m²/day have not been

evaluated in patients with CTCL. In clinical trials, bexarotene was administered for up to 118 weeks to patients with CTCL. Treatment should be continued as long as the patient is deriving benefit.

Paediatric population:

The safety and efficacy of bexarotene in children (aged below 18 years) have not been established. No data are available.

Elderly patients:

Of the total number of patients with CTCL in clinical studies, 61% were 60 years or older, while 30% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to bexarotene cannot be ruled out. The standard dose should be used in the elderly.

Patients with renal impairment:

No formal studies have been conducted in patients with renal insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the estimated renal clearance of bexarotene was less than 1 ml/minute. In view of the limited data, patients with renal insufficiency should be monitored carefully while on bexarotene therapy.

Method of administration

For oral use.

Targretin capsules should be taken as a single oral daily dose with a meal. The capsule should not be chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

Women of child-bearing potential without effective birth-control measures.

History of pancreatitis.

Uncontrolled hypercholesterolaemia.

Uncontrolled hypertriglyceridaemia.

Hypervitaminosis A.

Uncontrolled thyroid disease.

Hepatic insufficiency.

Ongoing systemic infection.

4.4 Special warnings and precautions for use

General: Targretin capsules should be used with caution in patients with a known hypersensitivity to retinoids. No clinical instances of cross-reactivity have been noted. Patients receiving bexarotene should not donate blood for transfusion. Butylated hydroxyanisole, an ingredient in Targretin, may cause irritation to the mucous membranes, therefore the capsules must be swallowed intact and not chewed.

Lipids: hyperlipidaemia has been identified as an effect associated with the use of bexarotene in clinical studies. Fasting blood lipid determinations (triglycerides and cholesterol) should be performed before bexarotene therapy is initiated and at weekly intervals until the lipid response to bexarotene is established, which usually occurs within two to four weeks, and then at intervals no less than monthly thereafter. Fasting triglycerides should be normal or normalised with appropriate intervention prior to bexarotene therapy. Every attempt should be made to maintain triglyceride levels below 4.52 mmol/l in order to reduce the risk of clinical sequelae. If fasting triglycerides are elevated or become elevated during treatment, institution of antilipaeamic therapy is recommended, and if necessary, dose reductions (from 300 mg/m²/day of bexarotene to 200 mg/m²/day, and if necessary to

100 mg/m²/day) or treatment discontinuation. Data from clinical studies indicate that bexarotene concentrations were not affected by concomitant administration of atorvastatin. However, concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene and therefore, concomitant administration of gemfibrozil with bexarotene is not recommended (see section 4.5). Elevations of serum cholesterol should be managed according to current medical practice.

Pancreatitis: acute pancreatitis associated with elevations of fasting serum triglycerides has been reported in clinical studies. Patients with CTCL having risk factors for pancreatitis (e.g., prior episodes of pancreatitis, uncontrolled hyperlipidaemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should not be treated with bexarotene, unless the potential benefit outweighs the risk.

Liver Function Test (LFT) abnormalities: LFT elevations associated with the use of bexarotene have been reported. Based on data from ongoing clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored weekly during the first month and then monthly thereafter. Consideration should be given to a suspension or discontinuation of bexarotene if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

Thyroid function test alterations: changes in thyroid function tests have been observed in patients receiving bexarotene, most often noted as a reversible reduction in thyroid hormone (total thyroxine [total T₄]) and thyroid-stimulating hormone (TSH) levels. Baseline thyroid function tests should be obtained and then monitored at least monthly during treatment and as indicated by the emergence of symptoms consistent with hypothyroidism. Patients with symptomatic hypothyroidism on bexarotene therapy have been treated with thyroid hormone supplements with resolution of symptoms.

Leucopenia: leucopenia associated with bexarotene therapy has been reported in clinical studies. The majority of cases resolved after dose reduction or discontinuation of treatment. Determination of white blood cell count with differential count should be obtained at baseline, weekly during the first month and then monthly thereafter.

Anaemia: anaemia associated with bexarotene therapy has been reported in clinical studies. Determination of haemoglobin should be obtained at baseline, weekly during the first month and then monthly thereafter. Decreases of haemoglobin should be managed according to current medical practice.

Lens opacities: following bexarotene treatment, some patients were observed to have previously undetected lens opacities or a change in pre-existing lens opacities unrelated to treatment duration or dose level of exposure. Given the high prevalence and natural rate of cataract formation in the older patient population represented in the clinical studies, there was no apparent association between the incidence of lens opacity formation and bexarotene administration. However, an adverse effect of long-term bexarotene treatment on lens opacity formation in humans has not been excluded. Any patient treated with bexarotene who experiences visual difficulties should have an appropriate ophthalmologic examination.

Vitamin A supplementation: because of the relationship of bexarotene to vitamin A, patients should be advised to limit vitamin A supplements to ≤15,000 IU/day to avoid potential additive toxic effects.

Patients with diabetes mellitus: caution should be exercised when administering bexarotene in patients using insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones). Based on the known mechanism of action, bexarotene may potentially enhance the action of these agents, resulting in hypoglycaemia. No cases of hypoglycaemia associated with the use of bexarotene as monotherapy have been reported.

Photosensitivity: the use of some retinoids has been associated with photosensitivity. Patients should be advised to minimise exposure to sunlight and avoid sun lamps during therapy with bexarotene, as *in vitro* data indicate that bexarotene may potentially have a photosensitising effect.

Oral contraceptives: bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestrogenic contraceptives. Thus, if treatment with bexarotene is intended in a woman of childbearing potential, a reliable, non-hormonal form of contraception is also required, because bexarotene belongs to a therapeutic class for which the human malformative risk is high.

Paediatric population:

Targretin is not recommended in children (aged below 18 years).

Targretin contains a small amount of sorbitol, therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on bexarotene: no formal studies to evaluate interactions with bexarotene have been conducted. On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4 (CYP3A4), coadministration with other CYP3A4 substrates such as ketoconazole, itraconazole, protease inhibitors, clarithromycin and erythromycin may theoretically lead to an increase in plasma bexarotene concentrations. Furthermore, co-administration with CYP3A4 inducers such as rifampicin, phenytoin, dexamethasone or phenobarbital may theoretically cause a reduction in plasma bexarotene concentrations.

Caution is advised in case of combination with CYP3A4 substrates having a narrow therapeutic margin i.e. immunosuppressive agents (cyclosporine, tacrolimus, sirolimus) as well as CYP3A4-metabolised cytotoxics, i.e. cyclophosphamide, etoposide, finasteride, ifosfamide, tamoxifen, vinca-alkaloids.

A population analysis of plasma bexarotene concentrations in patients with CTCL indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. The mechanism of this interaction is unknown. Under similar conditions, bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine. Concomitant administration of gemfibrozil with bexarotene is not recommended.

Effects of bexarotene on other substances: there are indications that bexarotene may induce CYP3A4. Therefore, repeated administration of bexarotene may result in an auto-induction of its own metabolism and, particularly at dose levels greater than 300 mg/m²/day, may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4, such as tamoxifen. For example bexarotene may reduce the efficacy of oral contraceptives (see sections 4.4 and 4.6).

Bexarotene may potentially enhance the action of insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones), resulting in hypoglycaemia (see section 4.4).

Laboratory test interactions: CA125 assay values in patients with ovarian cancer may be accentuated with bexarotene therapy.

Food interactions: in all clinical trials, patients were instructed to take Targretin capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and C_{max} values were substantially higher following the administration of a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data from clinical trials are based upon administration with food, it is recommended that Targretin capsules be administered with food.

On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4, grapefruit juice may theoretically lead to an increase in plasma bexarotene concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy: there are no adequate data from the use of bexarotene in pregnant women. Studies in animals have shown reproductive toxicity. Based on the comparison of animal and patient exposures to bexarotene, a margin of safety for human teratogenicity has not been demonstrated (see section 5.3). Bexarotene is contraindicated in pregnancy (see section 4.3).

If this medicinal product is used inadvertently during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential hazard to the foetus.

Contraception in males and females: women of childbearing potential must use adequate birth-control measures when bexarotene is used. A negative, sensitive, pregnancy test (e.g. serum beta-human chorionic gonadotropin, beta-HCG) should be obtained within one week prior to bexarotene therapy. Effective contraception must be used from the time of the negative pregnancy test through the initiation of therapy, during therapy and for at least one month following discontinuation of therapy. Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives (see section 4.5). Thus, if treatment with bexarotene is intended in a woman with childbearing potential, a reliable, non-hormonal contraceptive method is also recommended. Male patients with sexual partners who are pregnant, possibly pregnant, or may potentially become pregnant must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

Breast-feeding: it is unknown whether bexarotene is excreted in human milk. Bexarotene should not be used in breast-feeding mothers.

Fertility: there are no human data on the effect of bexarotene on fertility. In male dogs, some effects have been documented (see section 5.3). Effects on fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness and visual difficulties have been reported in patients taking Targretin. Patients who experience dizziness or visual difficulties during therapy must not drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile:

The safety of bexarotene has been examined in clinical studies of 193 patients with CTCL who received bexarotene for up to 118 weeks and in 420 non-CTCL cancer patients in other studies.

In 109 patients with CTCL treated at the recommended initial dose of 300 mg/m²/day, the most commonly reported adverse reactions to Targretin were hyperlipaemia ((primarily elevated triglycerides) 74%), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%).

b. Tabulated list of adverse reactions:

The following Targretin-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at the recommended initial dose of 300 mg/m²/day. The frequencies of

adverse reactions are classified as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Very common: Leucopenia
Common: Lymphoma Like Reaction, Lymphadenopathy, Hypochromic Anaemia^{1,2,3},
Uncommon: Blood Dyscrasia, Purpura, Coagulation Disorder, Coagulation Time Increased^{2,3},
Anaemia¹, Thrombocytopenia³, Thrombocythemia, Eosinophilia¹,
Leukocytosis², Lymphocytosis

Endocrine disorders

Very common: Hypothyroidism
Common: Thyroid Disorder
Uncommon: Hyperthyroidism

Metabolism and nutrition disorders

Very common: Hyperlipaemia, Hypercholesterolaemia
Common: Weight Gain, SGOT Increased, SGPT Increased, Lactic Dehydrogenase
Increased, Creatinine Increased, Hypoproteinaemia,
Uncommon: Gout, Bilirubinemia^{1,3}, BUN Increased¹, High Density Lipoprotein Decreased

Nervous system disorders

Common: Dizziness, Hypesthesia, Insomnia
Uncommon: Ataxia, Neuropathy, Vertigo, Hyperaesthesia, Depression^{1,2,3}, Agitation

Eye disorders

Common: Dry Eyes, Eye Disorder
Uncommon: Cataract Specified^{1,2,3}, Amblyopia³, Visual Field Defect, Corneal Lesion,
Abnormal Vision^{1,2,3}, Blepharitis, Conjunctivitis³

Ear and labyrinth disorders

Common: Deafness
Uncommon: Ear disorder

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Common: Peripheral Oedema
Uncommon: Haemorrhage, Hypertension, Oedema³, Vasodilatation^{1,2,3}, Varicose Vein

Gastrointestinal disorders

Common: Vomiting, Diarrhoea^{1,3}, Nausea³, Anorexia¹, Liver Function Tests Abnormal,
Cheilitis², Dry Mouth^{2,3}, Constipation, Flatulence,
Uncommon: Pancreatitis^{1,3}, Hepatic Failure, Gastrointestinal Disorder¹

Skin and subcutaneous tissue disorders

Very common: Exfoliative Dermatitis, Pruritus, Rash
Common: Skin Ulcer, Alopecia¹, Skin Hypertrophy, Skin Nodule, Acne, Sweating, Dry
Skin^{2,3}, Skin Disorder
Uncommon: Serous Drainage¹, Herpes Simplex, Pustular Rash, Skin Discoloration³ Hair
Disorder¹, Nail Disorder^{1,3}

Musculoskeletal and connective tissue disorders

Common: Bone Pain, Arthralgia, Myalgia

Uncommon: Myasthenia¹

Renal and urinary disorders

Uncommon: Albuminuria^{1,3}, Kidney Function Abnormal

General Disorders and administration site conditions

Very common: Pain, Headache, Asthenia

Common: Allergic Reaction, Infection, Chills¹, Abdominal Pain, Hormone Level Altered¹

Uncommon: Neoplasm, Fever^{1,2,3}, Cellulitis, Infection Parasitic, Mucous Membrane Disorder³, Back Pain^{1,2,3}, Lab Test Abnormal

1: adverse reactions noted with increased frequency when bexarotene was administered at a dose >300mg/m²/day.

2: adverse reactions noted with increased frequency when bexarotene was administered at a dose of 300 mg/m²/day in non-CTCL cancer patients.

3: adverse reactions noted with increased frequency when bexarotene was administered at a dose of >300 mg/m²/day (compared to administration to CTCL patients at 300 mg/m²/day) in non-CTCL cancer patients.

Additional adverse reactions observed when used outside of the recommended dose and indication (i.e. used in CTCL at an initial dose >300mg/m²/day or in non-CTCL cancer indications):

Newly observed adverse reactions: ecchymosis, petechia, abnormal white blood cells, thromboplastin decreased, abnormal erythrocytes, dehydration, increased gonadotrophic luteinizing hormone, weight loss, increased alkaline phosphatase, increased creatinine phosphokinase, lipase increased, hypercalcaemia, migraine, peripheral neuritis, paraesthesia, hypertonia, confusion, anxiety, emotional lability, somnolence, decreased libido, nervousness, night blindness, nystagmus, lacrimation disorder, tinnitus, taste perversion, chest pain, arrhythmia, peripheral vascular disorder, generalized oedema, haemoptysis, dyspnoea, increased cough, sinusitis, pharyngitis, dysphagia, mouth ulceration, oral moniliasis, stomatitis, dyspepsia, thirst, abnormal stools, eructation, vesicobullous rash, maculopapular rash, leg cramps, haematuria, flu syndrome, pelvic pain, and body odour.

Single observations of the following were also reported: bone marrow depression, decreased prothrombin, decreased gonadotrophic luteinizing hormone, increased amylase, hyponatraemia, hypokalaemia, hyperuricaemia, hypocholesterolaemia, hypolipidaemia, hypomagnesaemia, abnormal gait, stupor, circumoral paraesthesia, abnormal thinking, eye pain, hypovolaemia, subdural haematoma, congestive heart failure, palpitation, epistaxis, vascular anomaly, vascular disorder, pallor, pneumonia, respiratory disorder, lung disorder, pleural disorder, cholecystitis, liver damage, jaundice, cholestatic jaundice, melaena, vomiting, laryngismus, tenesmus, rhinitis, increased appetite, gingivitis, herpes zoster, psoriasis, furunculosis, contact dermatitis, seborrhoea, lichenoid dermatitis, arthritis, joint disorder, urinary retention, impaired urination, polyuria, nocturia, impotence, urine abnormality, breast enlargement, carcinoma, photosensitivity reaction, face oedema, malaise, viral infection, enlarged abdomen.

The majority of adverse reactions were noted at a higher incidence at doses greater than 300 mg/m²/day. Generally, these resolved without sequelae on dose reduction or withdrawal of treatment. However, among a total of 810 patients, including those without malignancy, treated with bexarotene, there were three serious adverse reactions with fatal outcome (acute pancreatitis, subdural haematoma and liver failure). Of these, liver failure, subsequently determined to be not related to bexarotene, was the only one to occur in a CTCL patient.

Hypothyroidism generally occurs 4-8 weeks after commencement of therapy. It may be asymptomatic and responds to treatment with thyroxine and resolves upon withdrawal of treatment.

Bexarotene has a different adverse reaction profile to other oral, non-retinoid X receptor (RXR) - selective retinoids. Owing to its primarily RXR-binding activity, bexarotene is less likely to cause mucocutaneous, nail, and hair toxicities; arthralgia; and myalgia; which are frequently reported with retinoic acid receptor (RAR) -binding agents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No clinical experience with an overdose of Targretin has been reported. Any overdose should be treated with supportive care for the signs and symptoms exhibited by the patient.

Doses up to 1000 mg/m²/day of bexarotene have been administered in clinical studies with no acute toxic effects. Single doses of 1500 mg/kg (9000 mg/m²) and 720 mg/kg (14,400 mg/m²) were tolerated without significant toxicity in rats and dogs, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX25

Mechanism of action

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs: α , β , and γ . Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the RARs.

In vitro, bexarotene inhibits the growth of tumour cell lines of haematopoietic and squamous cell origin. *In vivo*, bexarotene causes tumour regression in some animal models and prevents tumour induction in others. However, the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

Clinical results

Bexarotene capsules were evaluated in clinical trials of 193 patients with CTCL of whom 93 had advanced stage disease refractory to prior systemic therapy. Among the 61 patients treated at an initial dose of 300 mg/m²/day, the overall response rate, according to a global assessment by the physician, was 51% (31/61) with a clinical complete response rate of 3%. Responses were also determined by a composite score of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) which also considered all extracutaneous CTCL manifestations. The overall response rate according to this composite assessment was 31% (19/61) with a clinical complete response rate of 7% (4/61).

5.2 Pharmacokinetic properties

Absorption

Absorption/dose proportionality: pharmacokinetics were linear up to a dose of 650 mg/m². Terminal elimination half-life values were generally between one and three hours. Following repeat once daily dose administration at dose levels ≥ 230 mg/m², C_{max} and AUC in some patients were less than respective single dose values. No evidence of prolonged accumulation was observed. At the recommended initial daily-dose level (300 mg/m²), single-dose and repeated daily-dose bexarotene pharmacokinetic parameters were similar.

Distribution

Protein binding/distribution: bexarotene is highly bound (>99%) to plasma proteins. The uptake of bexarotene by organs or tissues has not been evaluated.

Biotransformation

Metabolism: bexarotene metabolites in plasma include 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest glucuronidation as a metabolic pathway, and that cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for formation of the oxidative metabolites. Based on the *in vitro* binding and the retinoid receptor activation profile of the metabolites, and on the relative amounts of individual metabolites in plasma, the metabolites have little impact on the pharmacological profile of retinoid receptor activation by bexarotene.

Elimination

Excretion: neither bexarotene nor its metabolites are excreted in urine in any appreciable amounts. The estimated renal clearance of bexarotene is less than 1 ml/minute. Renal excretion is not a significant elimination pathway for bexarotene.

Pharmacokinetics in Special Populations

Age: Based on the population pharmacokinetic analysis of data for 232 patients aged ≥ 65 years and 343 patients aged < 65 years, age has no statistically significant effect on bexarotene pharmacokinetics.

Body Weight and Gender: Based on the population pharmacokinetics analysis of data for 614 patients with a weight range of 26 to 145 kg, the bexarotene apparent clearance increases with increasing body weight. Gender has no statistically significant effect on bexarotene pharmacokinetics.

Race: Based on the population pharmacokinetic analysis of data for 540 Caucasian and 44 Black patients, bexarotene pharmacokinetics are similar in Blacks and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of bexarotene for other races.

5.3 Preclinical safety data

Bexarotene is not genotoxic. Carcinogenicity studies have not been conducted. Fertility studies have not been conducted; however, in sexually immature male dogs, reversible aspermatogenesis (28-day study) and testicular degeneration (91-day study) were seen. When bexarotene was administered for six months to sexually mature dogs, no testicular effects were seen. Effects on fertility cannot be excluded. Bexarotene, in common with the majority of retinoids, was teratogenic and embryotoxic in an animal test species at systemic exposures that are achievable clinically in humans. Irreversible cataracts involving the posterior area of the lens occurred in rats and dogs treated with bexarotene at systemic exposures that are achievable clinically in humans. The aetiology of this finding is unknown. An adverse effect of long-term bexarotene treatment on cataract formation in humans has not been excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

macrogol
polysorbate
povidone
butylated hydroxyanisole

Capsule shell:

gelatin
sorbitol special-glycerin blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water)
titanium dioxide (E171)
printing ink (SDA 35A alcohol (ethanol & ethyl acetate), propylene glycol (E1520), iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonium hydroxide 28%)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Keep the bottle tightly closed.

6.5 Nature and contents of container

High-density polyethylene bottles with child-resistant closures containing 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai Ltd.
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom
tel: +44 (0)208 600 1400
fax: +44 (0)208 600 1401
e-mail: EUmedinfo@eisai.net

8. MARKETING AUTHORISATION NUMBER

EU/1/01/178/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 March 2001.

Date of latest renewal: 29 March 2006.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Targretin 75 mg soft capsules
Bexarotene

2. STATEMENT OF ACTIVE SUBSTANCE

One capsule contains 75 mg of bexarotene.

3. LIST OF EXCIPIENTS

Contains sorbitol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 soft capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
To be swallowed whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd.
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/01/178/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY
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Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Targretin 75 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TARGRETIN 75 mg soft capsules Bexarotene

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Targretin is and what it is used for
2. What you need to know before you take Targretin
3. How to take Targretin
4. Possible side effects
5. How to store Targretin
6. Contents of the pack and other information

1. What Targretin is and what it is used for

The active substance in Targretin, bexarotene, belongs to a group of medicines known as retinoids, which are related to vitamin A.

Targretin capsules are used by patients with advanced stage cutaneous T-cell lymphoma (CTCL) whose disease has not responded to other therapies. CTCL is a condition in which certain cells of the body's lymph system called T-lymphocytes become cancerous and affect the skin.

2. What you need to know before you take Targretin

Do not take Targretin

- if you are allergic to bexarotene or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breast feeding or if you can become pregnant and are not using effective birth control measures.
- if you have a history of pancreatitis, have uncontrolled lipid (blood fats) elevations (high blood cholesterol or high blood triglycerides), have a condition known as hypervitaminosis A, have uncontrolled thyroid disease, have insufficient liver function or have an ongoing systemic infection.

Warnings and precautions

Talk to your doctor before taking Targretin if you have a known hypersensitivity to retinoids (related to vitamin A), suffer from liver disease, have high blood lipids or take medicines which may cause high blood lipids, have uncontrolled diabetes mellitus (sugar diabetes), have had gall bladder or biliary tract disease, or consume excessive amounts of alcohol.

Your fasting blood lipid determinations may have to be performed before therapy is initiated and at weekly intervals afterwards, and then monthly while taking this medicine.

Blood tests to evaluate the function of your liver and thyroid gland and to monitor your red blood cell and white blood cell counts will be obtained before therapy is started and will be monitored during therapy.

Periodic eye exams may be needed if you experience visual difficulties while taking this medicine.

Minimise exposure to sunlight as much as possible and avoid exposure to sun lamps.

Do not take more than 15,000 International Units of vitamin A supplements per day during treatment.

Children and adolescents

Targretin capsules should not be used in children or adolescents.

Other medicines and Targretin

Tell your doctor if you are taking, have recently taken or might take any other medicines, such as

- ketoconazole and itraconazole (used against fungal infections),
- erythromycin, clarithromycin and rifampicin (used against bacterial infections),
- phenytoin and phenobarbital (used against seizures),
- gemfibrozil (used to reduce high levels of fats in the blood such as triglycerides and cholesterol),
- vitamin A supplements, protease inhibitors (used against viral infections),
- tamoxifen (used against some forms of cancer),
- dexamethasone (used for inflammatory conditions),
- insulin, agents enhancing insulin secretion, or insulin-sensitisers (used against diabetes mellitus).

This is important as using more than one medicine at the same time can strengthen or weaken the effect of the medicines.

Targretin with food and drink

Targretin should be taken with food (see section 3). If you regularly consume grapefruit or grapefruit juice, please consult your doctor as these have the potential to alter your body's response to Targretin therapy.

Pregnancy and breast-feeding

Targretin may be harmful to a developing foetus. **DO NOT** use Targretin if you are pregnant or breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you are capable of becoming pregnant, you must have a pregnancy test within one week before you start therapy, confirming you are not pregnant. You must use effective contraception (birth control) continuously starting one month before beginning therapy until one month after you stop taking Targretin. It is recommended that two reliable forms of contraception be used together. If you are taking a hormonal contraceptive (for example, birth control pills), you should discuss this with your doctor.

If you are male and your partner is pregnant or capable of becoming pregnant, you must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

Driving and using machines

It is not known whether Targretin has an effect on your ability to drive a car or operate machinery. If you experience dizziness or problems with your vision during therapy, do not drive or operate machinery.

Targretin contains sorbitol and butylated hydroxyanisole

Targretin contains a small amount of sorbitol (a type of sugar). If you have an intolerance to some sugars, speak to your doctor before taking this medicinal product.

Butylated hydroxyanisole may cause irritation to the mucous membranes, therefore the capsules must be swallowed intact and not chewed.

3. How to take Targretin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The doctor will prescribe a suitable dose for you.

The recommended dose is generally 4 to 10 capsules to be taken once daily. Take your prescribed number of capsules at the same time each day with a meal. The capsules can be taken immediately before, during or immediately after the course of the meal, if preferred. The capsules should be swallowed whole and not chewed.

How long you should take Targretin

Although some patients have improvement within the first several weeks, most patients require several months or more of treatment to improve.

If you take more Targretin than you should

If you have taken more than the prescribed dose of Targretin, you must contact your doctor.

If you forget to take Targretin

If you forget to take one dose, take your daily dose with your next meal on the same day, then take your usual dose as normal, the following day. Do not take a double dose in one day to make up for a forgotten dose the previous day.

If you stop taking Targretin

Your doctor should determine how long you should take Targretin, and when treatment may be stopped. Do not stop taking your medication until your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor as soon as possible if you feel any deterioration in your condition while you are taking Targretin. Sometimes it is necessary to adjust the dose or interrupt treatment. Your doctor will advise you on what to do.

The following side effects were reported in patients with CTCL who were treated with the recommended initial dose of capsules.

Very common (can occur in more than 1 in 10 patients treated):

Low white blood cell count.

Lowering of thyroid hormones level.

Elevation of blood fats (triglycerides and cholesterol).

Skin reactions (Itching, redness, irritation, peeling).

Headache, fatigue, pain.

Common (can occur in up to 1 in 10 patients treated):

Low red blood cell count, enlarged lymph nodes, worsening of lymphoma.

Thyroid disorder.

Elevation of liver enzymes, impaired kidney function, low protein in blood, weight gain.

Insomnia, dizziness, reduced skin sensation.

Dry eyes, deafness, abnormal sensations of the eye including irritation and heaviness.

Swelling of legs and arms.

Nausea, diarrhoea, dry mouth, dry lips, loss of appetite, constipation, excess gas, abnormal liver function tests, vomiting.
Dry skin, skin disorder, loss of hair, skin ulcer, acne, skin thickening, skin nodule, increased sweating.
Joint aches, bone pain, muscle aches.
Chills, abdominal pain, allergic reaction, infection.

Uncommon (can occur in up to 1 in 100 patients treated):

Blood disorders, eosinophilia, leukocytosis, lymphocytosis, purpura, elevated and decreased numbers of blood platelets.
Overactive thyroid.
Elevated bilirubin in the blood, impaired kidney function, gout, decreased HDL cholesterol.
Agitation, difficulties with balance, depression, increased skin sensation on touching, abnormal nerve sensations, vertigo.
Abnormal vision, blurred vision, inflammation of the eye lids, cataract, inflammation of the white part of the eye, lesion of the cornea of the eye, ear disorder, defect in field of vision.
Swelling, bleeding, high blood pressure, fast heart rate, visible vein enlargement, dilation of blood vessels.
Gastrointestinal disorder, liver failure, inflammation of the pancreas.
Changes in hair, herpes simplex, nail disorder, pustular rash, serous drainage, skin discoloration.
Muscle weakness.
Proteins in urine, abnormal kidney function.
Back pain, skin infection, fever, parasitic infection, abnormal laboratory test, disorder of mucous membrane, tumour.

Rare fatal side effects are acute inflammation of the pancreas, bleeding in the head, and liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Targretin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Do not store above 30°C. Keep the bottle tightly closed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Targretin contains

Each Targretin capsule contains 75 mg of the active substance bexarotene.

The capsules also contain the other ingredients macrogol, polysorbate, povidone and butylated hydroxyanisole.

The capsule shell consists of gelatin, sorbitol special-glycerine blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water), titanium dioxide (E171) and printing ink (SDA 35A

alcohol (ethanol & ethyl acetate), propylene glycol (E1520), iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonium hydroxide 28%)

What Targretin looks like and contents of the pack

Targretin is available as soft capsules for oral use in a white plastic bottle containing 100 capsules.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Annex IV

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for bexarotene, the scientific conclusions of CHMP are as follows:

Following the review of a case of severe hypoglycemia after exposure in combination with a sulfonylurea (gliclazide) the PRAC considered further strengthening the current information on interactions between bexarotene and insulin, agents enhancing insulin secretion or insulin-sensitisers. Information about this interaction is currently mentioned in section 4.4 of the SmPC, but should also be mentioned in section 4.5 of the SmPC in line with the Guideline on Summary of Product Characteristics.

Therefore, in view of available data regarding interactions between bexarotene and insulin, agents enhancing insulin secretion or insulin-sensitisers, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for bexarotene the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing bexarotene is favourable subject to the proposed changes to the product information

The CHMP recommends that the terms of the Marketing Authorisation should be varied.